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# Internal and Cortical Border-Zone Infarction

## Clinical and Diffusion-Weighted Imaging Features

Seok Woo Yong, MD; Oh Young Bang, MD, PhD; Phil Hyu Lee, MD, PhD; Wen Yu Li, MD

**Background and Purpose**—The pathogenesis of internal border-zone (IBZ) and cortical border-zone (CBZ) infarcts is unclear. Both types of infarct have been combined into a single group in most previous reports, which has produced conflicting results. We hypothesized that different pathogenic mechanisms underlie IBZ and CBZ infarcts.

**Methods**—We reviewed 946 consecutive patients with ischemic stroke within the middle cerebral artery territory. IBZ and CBZ infarcts were selected based on diffusion-weighted imaging templates to identify vascular territories. Baseline patient characteristics, clinical courses, and neuroradiological features were compared between patients with IBZ and CBZ infarcts.

**Results**—We identified 45 IBZ and 75 CBZ infarct patients. Compared with the CBZ infarct patients, IBZ infarct patients had a higher degree of stenosis or occlusion in either the middle cerebral or internal carotid artery ( $P=0.008$ ) and exhibited a rosary-like pattern of infarction more frequently ( $P<0.001$ ). In contrast, concomitant small cortical infarcts were observed more frequently in CBZ infarct patients ( $P<0.001$ ). Clinical deterioration during the first 7 days of admission and poor outcome after 3 months after stroke was more prevalent in IBZ infarct patients than in CBZ infarct patients ( $P=0.002$  and  $P=0.003$ , respectively).

**Conclusions**—IBZ infarcts are caused mainly by hemodynamic compromise, whereas embolic pathogenesis appears to contribute greatly to the genesis of CBZ infarcts. Patients with IBZ infarcts showed poor early and late clinical courses. Our findings suggest that different therapeutic approaches may be required to prevent early clinical deterioration in patients with different types of border-zone infarcts. (*Stroke*. 2006;37:841-846.)

**Key Words:** hemodynamics ■ magnetic resonance imaging, diffusion-weighted ■ stroke, ischemic

Border-zone infarcts reportedly account for  $\approx 10\%$  of all brain infarcts.<sup>1</sup> It has long been debated whether border-zone infarcts are caused by impaired cerebral perfusion or by embolisms from the heart, aorta, and stenotic parent artery. Many reports<sup>2–10</sup> have emphasized that border-zone infarcts are the consequence of hemodynamic compromise (so-called low-flow infarcts), but other reports have suggested that this is not always the case and have insisted that embolization plays a major role in the development of border-zone infarcts.<sup>11–15</sup> Some studies have implicated both mechanisms in the pathogenesis of border-zone infarction; that is, reduced cerebral perfusion may impair the washing out of microemboli, which preferentially involves border-zone areas.<sup>16–20</sup> A possible explanation for the aforementioned discrepancies among different studies is that border-zone infarcts are heterogeneous and comprise 2 distinct types: hemodynamic compromise and microemboli.

A recent re-evaluation of the concept of border-zones led to the following classification: the internal border-zone (IBZ; internal junctional or subcortical border-zone) and cortical border-zone (CBZ; watershed, junctional, or external border-zone). Whether there are differences in pathogenesis associ-

ated with infarcts within the IBZ versus the CBZ is unclear because most relevant studies have been small and have either combined data for IBZ and CBZ infarcts into a single “border-zone infarct” group or focused on only 1 subtype of border-zone. As a result, it is not clear whether the mechanisms of stroke differ between IBZ and CBZ infarcts. Few studies<sup>21–24</sup> have focused on differences in the characteristics of each type of border-zone, and the results of these studies are inconsistent.

In the present study, we analyzed topographical differences detected using diffusion-weighted imaging (DWI) to classify border-zone infarcts as either IBZ or CBZ infarcts. We then made a comparative analysis of the clinical and neuroradiologic characteristics of patients in these 2 groups to determine whether the underlying pathogenesis differs between these 2 types of infarct.

### Methods

Patients registered in the Ajou Stroke Data Bank (Stroke Unit at Ajou University) between January 2000 and December 2004 who had an acute focal cerebral ischemic episode were included in the study if they met the following criteria: (1) they had focal neurologic

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symptoms and had been observed within 7 days of symptom onset; (2) they had relevant lesions within the middle cerebral artery (MCA) distribution territory on DWI; and (3) they had undergone a complete evaluation including medical history, vascular risk factors, routine blood tests, stroke scales, cardiologic workup (ECG and echocardiogram), and vascular studies.

T2-weighted imaging and DWI were performed for all patients (1.5 T; GE). Two authors (Y.S.W. and L.P.H.) who were blinded to the patient information reviewed the DWI data retrospectively and selected images that matched the border-zone area according to the commonly used templates.<sup>2</sup> IBZ infarcts were defined as hyperintense areas in the vascular IBZ, where the border between the deep and superficial perforating arterial territories of the MCA divides the infarct into 2 approximately equal sections.<sup>8</sup> Patients were classified as having a CBZ infarct if the DWI lesion mainly involved the border between the 2 main cerebral arteries, the border-zone area between the MCA and anterior cerebral artery, or the MCA and posterior cerebral artery.

To evaluate the frequency of concomitant embolic signals, we examined the presence of small cortical infarcts. A small cortical infarct was defined as a hyperintense DWI signal that was <10 mm and was located outside the border-zone area or centrum semiovale.<sup>25</sup> Extracranial and intracranial vascular status was evaluated, and the degree of stenosis was measured using a common method<sup>26–27</sup> and was graded as being mild (<50% stenosis), moderate (50% to 74% stenosis), severe (75% to 99%), or occluded.  $\kappa$  coefficient for interobserver agreement was 0.77 for the presence of an IBZ or a CBZ infarct and 0.74 for the degree of occlusion. The opinion of a neuroradiologist (Y.S.R.) was sought to resolve disagreements. The authors were blinded to the patient information through these processes.

Potential sources of cardioembolism (PSCE) were identified if any of the following existed: recent myocardial infarction (<3 weeks), atrial fibrillation, mitral stenosis, prosthetic valve, dilated cardiomyopathy, sick sinus syndrome, acute bacterial endocarditis, or patent foramen ovale. Patients without PSCE were designated as: (1) no significant stenosis (those with <50% stenosis in both internal carotid artery [ICA] and MCA); (2) ICA stenosis group (those with  $\geq$ 50% stenosis on the ICA); and (3) MCA stenosis group (those with <50% stenosis in the ICA and  $\geq$ 50% stenosis on the MCA). Characteristics on clinical presentation were assessed, including the presence of preceding transient ischemic attacks, any signs of cortical dysfunction, and lacunar syndromes. The National Institutes of Health Stroke Scale (NIHSS) score was checked serially at 1, 3, 5, and 7 days after admission. The clinical course was determined on the seventh day after admission and was defined as: (1) improved (NIHSS score decreased by  $\geq$ 2 points), (2) stable (NIHSS score decreased by <2 points), and (3) deteriorated (NIHSS score increased after admission). The outcome was investigated by determining the Modified Rankin Scale and Barthel Index at 3 months after stroke onset and was considered to be poor if the Modified Rankin Scale value was  $\geq$ 3 points or if the Barthel Index value was <60 points.<sup>28</sup>

Differences between the 2 groups were examined using a Pearson  $\chi^2$  test, Student *t* test, or Mann–Whitney test, depending on the nature of the variables being compared. Statistical significance was established at  $P < 0.05$ . Logistic regression analysis was applied to identify independent predictors of IBZ and CBZ infarcts. Independent variables were sex, age, vascular risk factors, PSCE, clinical course, the severity of stroke (NIHSS score at admission), the site of stenosis (MCA or ICA), the critical stenosis (stenosis degree  $>75\%$  or occlusion), and small cortical infarcts. The results are presented as an odds ratio (OR) as estimates of relative risk with a 95% CI.

## Results

Of 946 stroke patients, a border-zone infarct was observed in 120 (12.7%) patients of whom 67 (56%) were men and 53 (44%) were women. Among the 120 patients, 45 (38%) patients had IBZ infarcts and 75 (62%) had CBZ infarcts. Details of the clinical and demographic features of the

**TABLE 1. Clinical and Demographic Features in Patients With the IBZ and CBZ Infarcts**

Values	IBZ Infarcts (n=45)	CBZ Infarcts (n=75)	P
Male, n (%)	15 (33.3)	52 (69.3)	<0.001*
Age, y	65.9 $\pm$ 12.8	64.1 $\pm$ 12.3	NS
Risk factors, n			
Hypertension	34 (75.6)	41 (54.7)	0.022*
Diabetes	15 (33.3)	26 (34.7)	NS
Smoking	7 (15.6)	31 (41.3)	0.004*
Hyperlipidemia	14 (31.1)	26 (34.7)	NS
PSCE	7 (15.6)	10 (13.3)	NS
History of coronary artery disease	5 (11.1)	6 (8.0)	NS
History of stroke	9 (20.0)	21 (28.0)	NS
Laboratory data			
Hematocrit, %	39.2 $\pm$ 4.7	39.8 $\pm$ 5.1	NS
Glucose	157.4 $\pm$ 68.4	153.7 $\pm$ 73.3	NS
C-reactive protein	0.79 $\pm$ 2.3	0.68 $\pm$ 1.2	NS
Fibrinogen	393.1 $\pm$ 147.2	398.1 $\pm$ 162.3	NS
D-dimer	0.75 $\pm$ 1.38	0.54 $\pm$ 1.18	NS
Previous transient ischemic attack	1 (2.2)	8 (10.7)	NS
Cortical dysfunction	27 (60.0)	36 (48.0)	NS
Lacunar syndrome	8 (17.8)	13 (17.3)	NS
Initial NIHSS score	3.8 $\pm$ 3.5	3.6 $\pm$ 4.0	NS
Clinical course	n=45	n=75	0.002†
Improving	9 (20.0)	24 (32.0)	
Stable	17 (37.8)	42 (56.0)	
Deteriorated	19 (42.2)	9 (12.0)	
Hospital stay, d	17.8 $\pm$ 18.0	11.4 $\pm$ 13.2	0.018†
Prognosis at 90th day§	n=41	n=65	
Poor outcome, %	13 (31.7)	3 (4.6)	0.003*
Modified Rankin Score	2.2 $\pm$ 1.4	1.2 $\pm$ 1.2	<0.001†
Barthel Index	72.3 $\pm$ 31.7	92.2 $\pm$ 15.9	0.001†

\*Pearson  $\chi^2$  test; †*t* test; ‡Mann–Whitney test.

§Patients who recurred within 90th day were excluded (3 in the IBZ group and 9 in the CBZ group); 2 patients who refused to follow up were also excluded.

patients in each group are presented in Table 1. The male to female ratio was significantly higher in CBZ group than in the IBZ group ( $P < 0.001$ ). Among the risk factors, hypertension was more common in patients with IBZ infarcts ( $P = 0.022$ ), whereas current smoking was associated with CBZ infarcts ( $P = 0.004$ ). Other risk factors such as diabetes, PSCE, history of coronary artery disease or stroke, and serological results (including inflammation markers) did not differ between the groups.

The characteristics of clinical presentation at admission did not differ between the 2 groups. The frequencies of the presence of transient ischemic attacks before hospital visit, cortical dysfunctions, and lacunar symptoms were not different. Although NIHSS scores at the time of admission were not different between the groups, the clinical course during

**TABLE 2. Neuroradiological Characteristics of the IBZ and CBZ Infarcts**

Values	IBZ Infarcts (n=45)	CBZ Infarcts (n=75)	P
Timing of DWI from symptom onset, h	42.0±38.8	55.8±63.7	NS
Small cortical infarcts, n (%)			<0.001*
Absent	32 (71.1)	26 (34.7)	
Present	13 (28.9)	49 (65.3)	
Shape			
Oval or wedge-shaped	9 (20.0)	30 (40.0)	<0.001*
Rosary or chain-like	27 (60.0)	14 (18.7)	<0.001*
PSCE	7 (15.6)	10 (13.3)	NS
Site of stenosis ≥50% or occlusion†			
Absent	4 (8.9)	20 (26.7)	0.025*
ICA	10 (22.2)	24 (32.0)	NS
MCA‡	24 (53.3)	21 (28.0)	0.010*

\*Pearson  $\chi^2$  test; †those with PSCE are excluded; ‡those with ≥50% stenosis or occlusion on the MCA but no significant stenosis on proximal ICA.

the first 7 days of hospitalization was significantly different: only 12% of CBZ infarct patients deteriorated clinically during the first week compared with 42% of IBZ infarct patients; this resulted in a significantly longer hospital stay for patients in the latter group ( $P=0.018$ ). Among the 106 patients (88.3%) who were followed up at 3 months after stroke, significantly more patients with IBZ infarction had a poor outcome ( $P=0.003$ ). There was no mortality in both groups.

Details of the neuroradiologic characteristics of the 2 groups are presented in Table 2. Timing of DWI study from the symptom onset was not different between 2 groups. Small cortical infarcts were observed more frequently in CBZ infarct patients than in IBZ infarct patients ( $P<0.001$ ). Approximately 65.3% (49 of 75 patients) of the CBZ infarct patients had cortical spotted lesions, whereas no concomitant

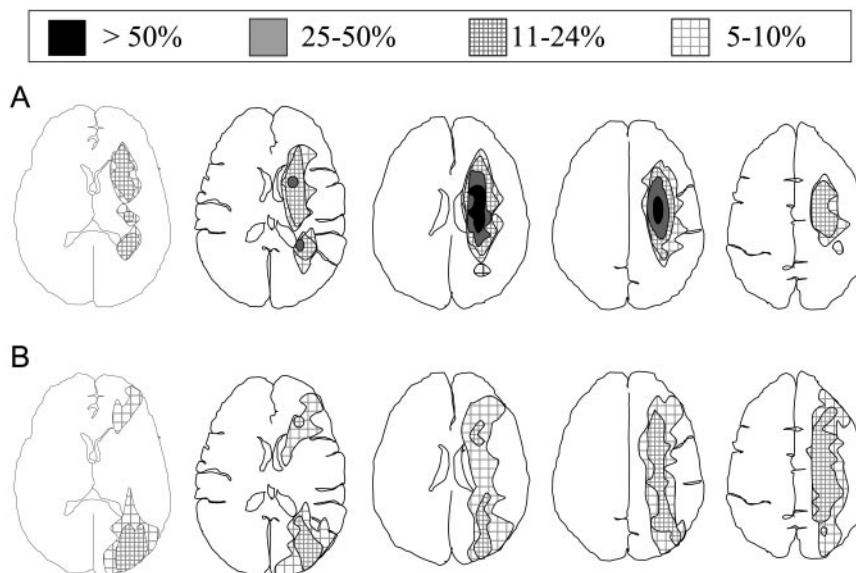
cortical lesions could be found in 71.1% (32 of 45 patients) of patients with the IBZ infarcts. CBZ infarcts tended to be oval or wedge-shaped (40%), whereas IBZ infarcts frequently assumed a chain-like or a rosary-like pattern (60%). A contour map of the frequencies of affected sites in each group is presented in Figure 1. It shows that the location of the IBZ varies along the lateral ventricle, whereas the CBZ is distributed more heterogeneously as wedged areas that extend from the frontal and occipital horn of the lateral ventricle or within the paramedian white matter at the supraventricular level.

Digital subtraction angiography was performed in 25 patients, magnetic resonance (MR) angiogram in 76 patients, and computed tomographic angiogram in 24 patients. According to the results of vessel imaging, more patients in the CBZ group were found to have no significant stenosis (8.9% versus 26.7%;  $P=0.025$ ). IBZ infarct patients more frequently had MCA stenosis without significant ICA stenosis (53.5% versus 28.0%;  $P=0.010$ ). When the degree of stenosis of symptomatic vessel was compared (Figure 2), IBZ infarct patients had significantly more severe stenosis compared with CBZ infarct patients ( $P=0.008$ ).

After adjustment for confounding factors, multivariate logistic regression analysis revealed that severe MCA stenosis or occlusion (OR, 5.05; 95% CI, 1.70 to 15.02;  $P=0.004$ ) and a deteriorating clinical course (OR, 7.85; 95% CI, 1.69 to 36.51;  $P=0.009$ ) were independently associated with the presence of an IBZ infarct. In contrast, being male (OR, 4.62; 95% CI, 1.55 to 14.14;  $P=0.006$ ) and the presence of small cortical infarcts (OR, 4.62; 95% CI, 1.57 to 13.55;  $P=0.005$ ) were independently associated with the presence of a CBZ infarct.

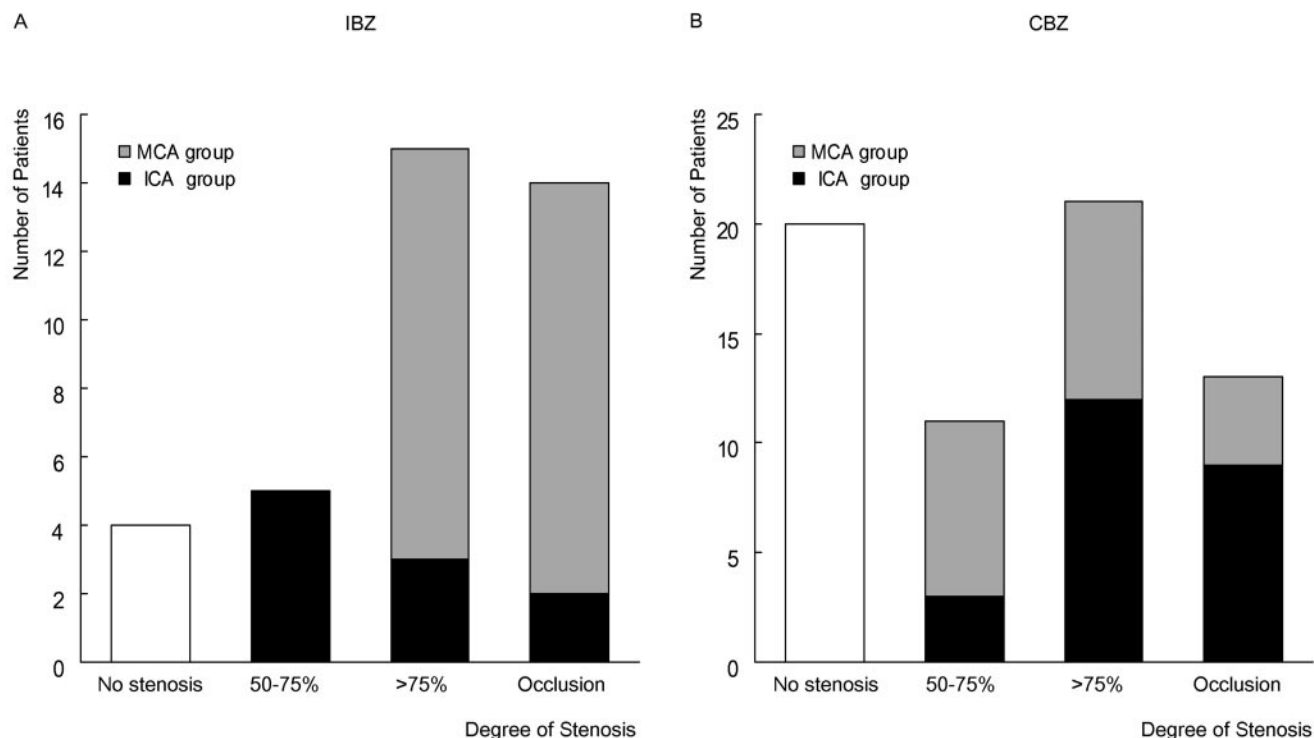
## Discussion

Border-zone infarction was traditionally thought to be caused by hemodynamic compromise attributable either to severe stenosis in large arteries (especially the ICA) or acute hypotensive events such as cardiopulmonary bypass. Many studies of the pathogenesis of border-zone infarcts have advocated this theory<sup>2-10</sup> based on findings such as more



**Figure 1.** Contour map of frequency of affected sites in the IBZ (A) and CBZ (B) infarcts. The location of the IBZ can vary along the lateral ventricle, whereas the CBZ is distributed more heterogeneously as wedged areas that extend from the frontal and occipital horn of the lateral ventricle or within the paramedian white matter at the supraventricular level.





**Figure 2.** Comparison of stenosis degree of the symptomatic vessels in IBZ (A) and CBZ (B) groups. Patients with PSCE are excluded. IBZ infarct patients has significantly more severe stenosis compared with CBZ infarct patients ( $P=0.008$  on Mann-Whitney test).

frequent and severe arterial stenosis in border-zone infarct patients, increased regional oxygen extraction, and decreased regional cerebral blood flow on positron emission tomography, and other evidences via carotid Doppler imaging, MR perfusion, or MR spectroscopy.

Microembolism either from the heart or stenotic arteries has been postulated to be an alternative cause of border-zone infarcts.<sup>11–15</sup> The results of an autopsy series revealed that embolic materials were observed frequently within border-zone areas that contained infarcts.<sup>11,13</sup> There is also an experimentally proven case of border-zone infarct induced by microemboli,<sup>12</sup> which suggests that microemboli preferentially propagate to border-zone areas. Caplan et al<sup>16</sup> suggested that hemodynamic compromise and microembolism collaborate in the pathogenesis of border-zone infarcts; that is, reduced perfusion limits the ability of the bloodstream to wash out emboli, particularly within the border-zone. Several reports<sup>17–20</sup> concur with this idea, with only 1 of these reports<sup>20</sup> objectively identifying the role of microemboli by means of signal monitoring with transcranial Doppler; others<sup>17–19</sup> have based their arguments on the fact that intracranial stenosis was not consistently found.

The inconsistency in defining the pathophysiology of border-zone infarcts may be the result of the following. First, because of the lack of DWI data, chronic infarcts were not separated from acute infarcts in most studies.<sup>2–10,12–14,17</sup> To date, DWI has been used for this purpose in only 4 studies.<sup>15,18–20</sup> Second, most reports have been focused on stenosis in the ICA<sup>2–5,7–10,15,19</sup> and have directed relatively little attention to MCA stenosis. Perhaps the most important reason is that many previous reports have combined infarcts within

the IBZ and those within the CBZ into a single group under the implicit assumption that infarcts in these 2 border-zones are caused by the same mechanism.<sup>2,5,7,10,15,17–20</sup> Moreover, in many reports, either only IBZ<sup>4,6,8</sup> or CBZ<sup>3,9,14</sup> infarcts were selectively included. Thus, the results of such studies are only partially relevant to the aspects of border-zone infarcts and cannot be used for generalization.

To the best of our knowledge, only 4 studies have explicitly examined differences in the pathophysiology of IBZ and CBZ infarctions<sup>21–24</sup> (see the supplemental Table I, available online at <http://stroke.ahajournals.org>). None of these studies used DWI, and 3 of them were carried out under the context of carotid stenosis or occlusion. All studies but 1 demonstrated that only IBZ infarcts are directly related to hemodynamic disturbance. Among the studies of the pathogenesis of border-zone infarcts, this study is the largest (120 patients) to date and 1 of the few studies in which DWI and demographic and clinical data have been compared.

The results of our study revealed an association between the presence of IBZ infarcts and hemodynamic compromise, whereas this relationship was less obvious in patients with CBZ infarcts. IBZ infarcts were associated with severe stenosis (stenosis degree  $\geq 75\%$ ) or occlusion in MCA (24 patients) or ICA (5 patients) which accounted for  $\approx 76.3\%$  of IBZ infarct patients without PSCE (Figure 2). IBZ infarcts were more frequently associated with a rosary-like pattern of infarcts, which is believed to be indicative of hemodynamic failure.<sup>24,29</sup> Small cortical infarcts, which are thought to represent embolic infarcts that originate in the heart or large arteries,<sup>25</sup> were not found in  $>70\%$  of the IBZ infarct patients. These findings all support the idea that a hemodynamic mechanism is the main cause of IBZ infarcts.

Compared with patients with IBZ infarcts, patients with CBZ infarcts had a rosary-like pattern less frequently. Moreover, about two-thirds of CBZ infarct patients had concomitant small cortical infarcts. Only  $\approx 52.3\%$  of CBZ infarct patients had severe stenosis or occlusion of symptomatic vessel compared with 76.3% of IBZ infarct patients (Figure 2). Mild or moderate carotid artery stenosis is unlikely to cause hemodynamic disturbances. In fact, a lower degree of ICA stenosis is associated with disseminated small embolic lesions on DWI,<sup>19</sup> whereas a high degree of stenosis ( $>90\%$ ) is associated with fewer embolic signals detected by transcranial Doppler ultrasonography.<sup>30</sup> These findings all support the idea that an embolic mechanism plays a crucial role in the pathogenesis of CBZ infarcts.

The relatively greater vulnerability of the IBZ to a decrease in cerebral perfusion has been ascribed to the anatomical characteristics of cerebral arterioles within this area. The perforating medullary arteries from the pial arteries that reach the IBZ area are the most distal branches of the ICA, and perfusion pressure is likely to be the lowest in these distal arteries.<sup>31</sup> In addition, lenticulostriate arteries have relatively little collateral blood supply. Perfusion studies have demonstrated that paraventricular white matter is most vulnerable to hemodynamic changes in patients with carotid artery occlusive disease.<sup>32</sup> The CBZ lies relatively closer to the cortical surface, where penetrating arteries originate, and has better chance for collateral supply through leptomeningeal and dural anastomoses, which makes it more resistant to decreased cerebral perfusion.

In the present study, we demonstrated that patients with IBZ infarcts showed worse hospital courses and remained severely disabled state at 3 months after stroke. In contrast, our patients with CBZ infarcts had a relatively benign clinical course. These results suggest that more intensive care is warranted in the initial stages of an IBZ infarct, with the aim of ameliorating the vascular insufficiency. In contrast, many of CBZ infarct patients may suffice with therapeutic approaches such as antiplatelet agents and statins that reduce microembolism and stabilize atheromatous plaques.

This study has several limitations. This is a retrospective study, hence the vascular imaging modalities were not homogenous. We identified border-zone infarcts using DWI imaging, which is the most accurate method of defining the size and location of ischemic stroke at present. However, because vascular territories may vary greatly among individuals,<sup>17,33</sup> the location of border-zone is sometimes hard to define. This study was undertaken in the Asian population, in which MCA stenosis is more prevalent. The result may not be identical in areas where intracranial stenosis is less often found, and a portion of IBZ infarction patients who have intracranial stenosis is likely to be not so much as high as 53% as in our study. We used the presence of small cortical infarcts as a marker of embolic stroke. Future investigations with transcranial Doppler ultrasonography monitoring for high-intensity transient signals would allow embolic sources to be identified more specifically. Also, perfusion images and follow-up DWI would be helpful.

In conclusion, IBZ infarcts appear to be caused mainly by hemodynamic compromise and are frequently associated

with clinical deterioration. In contrast, embolic pathogenesis appears to contribute substantially to the genesis of CBZ infarcts. These findings suggest that patients with different types of border-zone infarct would require different therapeutic approaches to prevent early clinical deterioration.

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